Synaptic Drive

In this module we will derive the form for the conductance dynamics on the post-synaptic side of the synapse and use this to calculate the current and voltage response. The statistics of vesicle release on the pre-synaptic side will be examined with vesicle run down shown to lead to synaptic depression.

Mathematical Physiology, Keener and Sneyd. Chapter 7 p216-236. Springer.
Theoretical Neuroscience, Dayan and Abbott. Chapter 5 p178-189. MIT Press
Spiking Neuron Models, Gerstner and Kistler. Chapter 2 p51-53. Cambridge Univeristy Press
Methods in Neuronal Modelling, Koch and Segev. Chapter 1 p1-p25. MIT Press

• Time-course of the Post-Synaptic Conductance and Current
It is assumed that at $t = 0$ a vesicle is released and neurotransmitter floods the synaptic cleft. Let there be N post-synaptic channels, where the channel can be in one of two states: open O with $x = 1$ or closed C with $x = 0$. The total number of open channels can be written

$$X = \sum_{k=1}^{N} x_k \quad \text{and} \quad \beta = \text{closing rate } 1 \to 0. \tag{1}$$

When the neurotransmitter is released at the synapse all the channels are opened instantaneously so that initially $x_k = 1 \; \forall \; k$. These channels then start to close at a rate β and it is also assumed that the neurotransmitter is quickly removed from the cleft so there are no further openings of any channels that might have already closed. Writing an equation for X and assuming the average gives a good indication of the behaviour, so that $X \simeq N\langle x \rangle$, we have

$$\frac{d\langle x \rangle}{dt} = -\beta \langle x \rangle \quad \text{with solution} \quad \langle x \rangle = e^{-t\beta} \tag{2}$$

where the factors of N have been dropped from both sides. It is more usual to write the factor in the exponent in terms of a closing time constant (synaptic-type dependent) which we will call $\tau_s = 1/\beta$. In this way the total time-dependent synaptic conductance and current can be written

$$g_s(t) = \overline{g_s} e^{-t/\tau_s} \quad \text{and} \quad I = \overline{g_s}(E_s - V) e^{-t/\tau_s} \tag{3}$$

where $\overline{g_s} = \gamma N$ is the maximum conductance of the synapse with γ the conductance of a single channel. It should be noted that the synaptic current is written in a form that is $-I_{ion}$. This is because it is considered a driving term and usually appears on the right-hand side of the voltage equation.

The types of fast synapses that are most often considered are: excitatory AMPA synapses that have a reversal $E_e = 0$mV, due to the fact that both Na^+ and K^+ flow through them, a time constant of $\tau_e = 3$ms and a strength $\overline{g}_e = 0.1 - 1$nS; and inhibitory $GABA_A$ synapses that have a reversal $E_i = -70$mV, because the channels carry Cl^- ions, a time constant $\tau_i = 10$ms and a conductance $\overline{g}_i = 0.1 - 1$nS. Note that the conductances here are in absolute units, not per unit area.

The current due to a synaptic impulse is called the Post-Synaptic-Current, or PSC. For excitatory events one writes EPSC and for inhibitory IPSC.

• The Post-Synaptic Voltage Response to a Synaptic Current Pulse

We will now calculate the effect of this current on the voltage. The voltage equation for a neuron with a leaky membrane can be written

$$C\frac{dV}{dt} = g_L(E_L - V) + I \tag{4}$$

where now the capacitance C and leak conductance g_L are the total values for the cell (not per unit area). Inserting the form of the synaptic current and dividing by g_L allows the equation to be written

$$\tau_L\frac{dV}{dt} = E_L - V + \frac{\overline{g}_s}{g_L}(E_s - V)e^{-t/\tau_s}. \tag{5}$$

This equation can be solved for the voltage $V(t)$ but the form is inconvenient for analysis. An accurate approximation can be made by noting that the synaptic conductance is usually much less than the total conductance of the cell, and hence $\overline{g}_s/g_L$ is small. The voltage can be written as $V = E_L + v$ where v is of the order of $\overline{g}_s/g_L$. Inserting this voltage into the equation

$$\tau_L\frac{dv}{dt} = -v + \frac{\overline{g}_s}{g_L}(E_s - E_L)e^{-t/\tau_s} + O(v\frac{\overline{g}_s}{g_L}). \tag{6}$$

Dropping the second order term and integrating for v gives

$$v = \frac{\overline{g}_s}{g_L}(E_s - E_L)\int_0^t \frac{dt'}{\tau_L}e^{-(t-t')/\tau_L}e^{-t'/\tau_s}. \tag{7}$$

Performing the integration and substituting back for the voltage $V(t)$ yields

$$V = E_L + \frac{\overline{g}_s}{g_L}(E_s - E_L)\frac{\tau_s}{\tau_L - \tau_s}\left(e^{-t/\tau_L} - e^{-t/\tau_s}\right). \tag{8}$$

The voltage response to a synaptic pulse can be written as the difference of two exponentials with time constants $\tau_L \simeq 20$ms and τ_s being either $\tau_e = 3$ms or $\tau_i = 10$ms depending on whether the synapse is an excitatory AMPA synapse or inhibitory GABA_A synapse.

This waveform is called a Post-Synaptic Potential, or PSP: for excitatory synapses an EPSP and for inhibitory synapses an IPSP.

• Statistics of Pre-Synaptic Vesicle Release

We now turn our attention to the pre-synaptic terminal. Let us assume that there are n contacts from a presynaptic neuron onto the postsynaptic cell and that each contact is able to release at most one vesicle per presynaptic action potential. Let the probability that a vesicle is released on the arrival of an action potential be p. The probability that k vesicles, out of a maximum number n, are released is given by the binomial distribution

$$P_k = \frac{n!}{k!(n-k)!}p^k(1-p)^{n-k}. \tag{9}$$

For pyramidal-to-pyramidal cell connections $p \simeq 0.6 - 0.8$. It is interesting to examine the probability there is a failure $P_0 = (1-p)^n$. For $p = 0.6$ and $n = 1, 2$ and 4 the fraction of a release failures are 40%, 16% and 2.6% respectively. The number of release sites is typically quoted at around $n = 5 - 10$. Hence it is unlikely to see a release failure with an isolated pulse.

• Post-Synaptic Amplitude Distribution

We now consider the distribution of amplitudes on the post-synaptic side, which are proportional to the amount of neurotransmitter released. We assume that a vesicle contains an amount of neurotransmitter that is Gaussian distributed so that the average voltage amplitude for a single vesicle is a with a standard deviation of σ_a. We can then make use of the relation for addition of Gaussian random numbers: for k vesicles

$$\text{the mean} = ka \quad \text{and} \quad \text{the variance} = k\sigma_a^2 \tag{10}$$

Hence, if k vesicles are released the amplitude distribution is expected to be

$$\rho_k(A) = \frac{1}{\sqrt{2\pi k\sigma_a^2}} \exp\left(\frac{-(A-ka)^2}{2k\sigma_a^2}\right). \tag{11}$$

The number of vesicles released is, however, binomially distributed, so that the full distribution can be written

$$P(A) = \delta(A)P_0 + \sum_{k=1}^{N} \rho_k(A)P_k \tag{12}$$

where $\delta(A)$ is the Dirac delta function and P_k was given in equation (9). This formula is important because it relates an observable, the post-synaptic voltage distribution, to the number of vesicles and their size which are hard to measure directly. The distribution (12) can give a very accurate fit to data with the quantal effects clearly visible in the multi-modal distribution.

• Vesicle Run Down: Synaptic Depression

The analysis above was for the case of voltage amplitudes measured from synaptic events that are well separated, such that there is always sufficient time for a new vesicle to be moved into place before the next presynaptic spike arrives. We will now consider the response to a train of presynaptic spikes that start at time $t = 0$ and continue at intervals of Δ. Let D_m be the probability that a vesicle is present at the contact in question before the arrival of the mth spike. This means that the probability that a vesicle is released at the arrival of the mth spike is $p_m = pD_m$. The initial conditions mean that $D_1 = 1$. We also assume that after a vesicle is released, it is restocked at a rate $1/\tau_D$. For synapses that show synaptic depression (such as between pyramidal cells) the time constant τ_D is usually around 500ms. Hence the probability that a release site remains empty for a time Δ is

$$P(\text{remains empty}) = e^{-\Delta/\tau_D} \quad \text{so that} \quad P(\text{empty and then refilled}) = 1 - e^{-\Delta/\tau_D}. \tag{13}$$

With these definitions, we can derive a formula that links the probability that a vesicle is ready to be released just before the m and $m+1$ presynaptic spikes arrive. The relation is

$$D_{m+1} = (1-p)D_m + pD_m(1-e^{-\Delta/\tau_D}) + (1-D_m)(1-e^{-\Delta/\tau_D}). \tag{14}$$

On the RHS: the first term is the chance that before spike m there was already a vesicle, and it was not released; the second term is the chance that there was a vesicle before the mth spike, it was released, but was then restocked before the $(m+1)$th spike arrived; and the third term is the probability that there was no vesicle ready before spike m but that the site was restocked before the $(m+1)$th spike. Combining terms gives,

$$D_{m+1} = D_m\left((1-p)e^{-\Delta/\tau_D}\right) + \left(1-e^{-\Delta/\tau_D}\right) = D_m\beta + \alpha \tag{15}$$

If $\Delta \to \infty$ or $\tau_D \to 0$ then $D_m \to 1$ as expected. We now calculate the long-time limit, after many presynaptic spikes. When this occurrs $D_{m+1} = D_m = D_\infty$, hence

$$D_\infty = \frac{\alpha}{1-\beta} = \frac{1-e^{-\Delta/\tau_D}}{1-(1-p)e^{-\Delta/\tau_D}} \quad \text{NB if } \Delta \ll \tau_D \text{ then} \quad D_\infty \simeq \frac{\Delta}{p\tau_D}. \tag{16}$$

We now calculate the dynamical approach to this steady state by introducing the excess $d_m = D_m - D_\infty$. Inserting this into equation (15)

$$d_{m+1} + \frac{\alpha}{1-\beta} = d_m\beta + \frac{\beta\alpha}{1-\beta} + \alpha \quad \text{so that} \quad d_{m+1} = d_m\beta \quad \text{with solution} \quad d_m = A\beta^m. \tag{17}$$

Hence the relaxation to the steady state is exponential. On using the initial condition the prefactor A can be fixed so that

$$D_m = (1-D_\infty)\beta^{m-1} + D_\infty. \tag{18}$$

From this we get the release probability $p_m = pD_m$. Across the n release sites, the probability that a vesicle is released is still binomial, hence for k particles

$$P_k = \frac{n!}{k!(n-k)!} p_m^k (1-p_m)^{n-k}. \tag{19}$$

The probabiltiy of a release failure is $P_0 = (1-p_m)^n$. For a high rate of spike arrival (when $\Delta \ll \tau_D$ - see also Eq 16) we have $p_\infty = pD_\infty = \Delta/\tau_D$. Hence for $\tau_D = 500$ms and $\Delta = 100$ms (i.e. 10Hz) we have for $n = 1, 2$ and 4 release failure probabilities of 80%, 64% and 41%. Hence, transmission failures represent a potentially significant source of noise at active synapses.

• Synaptic Communication at High Input Frequencies

The total current delivered to the neuron via an active synapse is now examined for the regular presynaptic spiking case that was considered above. The total current delivered is proportional to the product of two factors; (i) the strength of the synapse (i.e. the number of vesicles released per presynaptic spike) which for long time limits is proportional to D_∞; and (ii) the rate $1/\Delta$ at which the synapses are activated and vesicles have a chance of being released

$$I_{syn} \propto D_\infty/\Delta \sim \frac{1}{p\tau_D} \tag{20}$$

where the second result is for the high-frequency case (see Eq. 16). It can be noted, then, that in the high-frequency limit the total amount of current delivered is independent of the frequency that the presynaptic neuron fires: no information about the firing rate of the presynaptic neuron is transferred for high-frequency regular firing. So what information does the synapse transfer?

Consider a long period of presynaptic firing at a rate $1/\Delta_1$ so that the steady state is reached $D_{\infty 1} = \Delta_1/p\tau_D$. Now assume that the firing rate is increased to $1/\Delta_2$ at a time T where $\Delta_2 < \Delta_1$. The vesicle occupancy D_m will relax exponentially and smoothly (starting at its old value of $D_{\infty 1}$) to the new lower value $D_{\infty 2} = \Delta_2/p\tau_D$. If we now consider the current arriving in the postsynaptic cell we have

$$I_{syn} \propto D_{\infty 1}/\Delta_1 \sim \frac{1}{p\tau_D} \quad \text{before } T \tag{21}$$

$$I_{syn} \propto D_{\infty 1}/\Delta_2 \sim \frac{\Delta_1}{\Delta_2}\frac{1}{p\tau_D} \quad \text{just after } T \tag{22}$$

$$I_{syn} \propto D_{\infty 2}/\Delta_2 \sim \frac{1}{p\tau_D} \quad \text{long after } T. \tag{23}$$

Because $\Delta_1/\Delta_2 > 1$ the current just after the change in frequency will be transiently stronger. Similarly if the new firing rate $1/\Delta_2$ would have been lower there would have been a weaker transient current just after the change in frequency. This analysis shows that, at high frequencies of presynaptic spike arrival, a synapse with synaptic depression (or vesicle run-down) communicates information only about *changes* in the signal - its acts as a natural differentiator.

Though not considered in any detail in this course, there exists another type of short-term synaptic dynamics called *facilitation*. For synapses that facilitate, the initial probability of release p is very low, but as Calcium builds up in the presynaptic terminal, after many spikes arrive, p can increase dramatically and so the response gets progressively stronger.